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## Comment

# Homeostasis and the fuelling of metabolism

## Comment on “Physics of metabolic organization” by Marko Jusup et al.

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The nice and lucid introduction by Jusup et al. [2] to the standard model of Dynamic Energy Budget (DEB) theory aims, according to the authors, to serve both physicists and biologists. In my opinion, the authors have been very successful in this, and even for me, as founder of DEB theory, I found several new elements (see below).

The standard DEB model is the simplest non-degenerated model in the family of models in the context of DEB theory. I see it as a canonical form, and applies to most animals (see [1]). This is because animals are special organisms in the sense that they feed on other organisms, dead or alive, so a chemically complex substrate that covers all their metabolic needs. The differences in chemical composition between prey species for animals are less important than their amounts. Many organisms acquire the various substrates (energy, carbon, nutrients) independently of each other. The number of required reserves should match the number of independently acquired substrates to smooth out fluctuations in availability in the environment [5]. A single reserve is thus an evolutionary advanced situation [7]. Multiple reserves, required for most other organisms, come with additional complexity of linking their dynamics to respect stoichiometric constraints, involving some excretion of (transformed) reserve. I only learned how to get there in a natural way, after the discovery of Synthesizing Units (SUs) [4], basically a re-formulation of enzyme kinetics that avoids the use of the concept concentration and is fully based on fluxes.

Although the standard DEB model might seem complex to some, I think that it is extremely simple, given the complexity of its task to capture a bewildering biodiversity that exists. In my opinion it is not possible to strip it down any further, simplicity has been my top priority during its development, without substantially loosing performance to match data and to compare species on the basis of their parameter values, while still respecting biodiversity. I agree with the authors that the DEB book [6] may be hard to read for physicists and mathematicians because of the many biological ‘details’. Being aware of the existing biodiversity, I constantly heard voices from my fellow biologists in the back of my mind while writing the book saying ‘This is nonsense, don’t you know of the existence of this or that species that does it differently?’. This would be a natural critique when you have the ambitious aim of capturing all life in one framework. I also thought that the details help to match the real and the abstract worlds, a key operation for modelling. My experience is that the ‘details’ easily confuse newcomers to the line of thinking, so I admire the courage of Jusup et al. to strip most of them which makes it more easy to start with.

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## 1. Homeostasis

Generally, I see two different, complementary, strategies to deal with quantitative aspects of metabolism: the molecular and the pool approach. The molecular approach follows molecules. Since there are many different types of molecules, one is forced to select a few important ones that are followed in models; the many unimportant ones are not followed. I never saw convincing examples where models with many variables and parameters contributed to understanding and prediction, so to follow them all is not an option. Since molecules transform to other ones, this approach is very difficult, if not impossible, to combine with exploiting mass conservation. Moreover, the dynamics of molecules is strongly complicated by spatial structure, where membranes play a key role in metabolism and well-mixedness of cytoplasm and diffusion-based reactions are illusions in living cells.

The pool approach delineates a limited number of pools (called strong homeostasis), i.e. mixtures of chemical compounds that do not change in composition, but can change in mass. The general idea is to reduce the number of pools as much as possible. If one would delineate a single pool in an individual, which can be called biomass, no changes in chemical composition can be accommodated, nor the notion of metabolic memory, i.e. the nutritional state of an individual. The latter I consider to be essential to understand what organisms are actually doing, so we need at least two pools; [6] gives more reasons to work with at least 2 pools. Although pools are easy to combine with exploiting mass conservation and also with stoichiometric constraints on transformations, they are obviously a stylised idealisation of a complex reality that also complicates direct links with the molecular level: any particular molecule in a body can belong to any of the pools, it is the dynamics that matters.

So each of the two strategies have their own strengths and weaknesses. I found it surprising how well predictions from the pool approach match data, given the extreme simplicity of its assumptions. If we really want to specify the thermodynamics of an individual, we have to deal with entropies. We can only access the entropy of living biomass, if we have the full energy balance during ontogeny. We can only obtain the full energy balance, however, if we have the full mass balance. This for me means, that this is only possible in the pool approach, and also that we need all these conservation principles simultaneously. This already gives a minimum level of required complexity.

DEB theory exploits all sorts of conservation principles actively. It has, for instance, no assumptions about respiration, but obtains heat dissipation, dioxygen consumption (in aerobic situations), carbon dioxide, water and nitrogen-waste production from closing the conservation of energy and the 4 leading chemical elements in living matter. This does not mean, however, that DEB theory ignores transportation constraints on respiration, since the interaction between surface areas and volumes is key to the dynamics of pools in DEB theory, from which respiration derives.

The moment that I realised that DEB theory was generally applicable came when I discovered implied rules for the covariation of parameter values [3]. These rules were purely based on the physical interpretation of its parameters in being intensive or extensive and can be used to understand that respiration of fully grown adults should scale with body weight to the power somewhere around  $3/4$  among species. To understand this well-known empirical pattern has been a major challenge in the eco-physiological literature for a long time. It was a big relief for me, since if the implications of the model would be at odds with this empirical pattern, it would be useless in ecosystem applications.

Yet another puzzle kept me busy since the beginning: to understand the supply-demand spectrum. Growth and reproduction seem to be pre-programmed in some species (mainly birds and mammals), and they eat what they need to cover the costs. Other species, however, seem to be much more flexible in this and eat just dependent on food availability. Over the years I saw an increasing number of physiological properties that have a direct link with where species are on the supply-demand spectrum. Demand species evolved from supply species, but how could a single model capture both extremes? It took me 35 years to understand that the answer to this question has been staring at me right from the beginning, but I did not see it until recently [8]. After the scaling relations, the quantification of this spectrum was for me the most important finding of DEB theory, which also gave simple access to the physical boundaries of the parameter and the data space, and to find bijections between both spaces, which we now exploit in parameter estimation.

## 2. Reserve mobilisation

The most important new element in the Jusup et al. paper for me is, without doubt, the derivation of reserve mobilisation, the fuelling of metabolism, which I see as a cornerstone of the theory. Back in the late 70's, I reformulated

the static empirical model by Droop on cell quota (for nutrients in algae during steady states in chemostats) in terms of a dynamic one (for reserve in animals during ontogeny), accounting for maintenance and isomorphy. I was directly satisfied with its behaviour, it did not change since then, but not at all with how it followed from assumptions, since I tried to build a theory on first principles with no empirical elements. The scientific value of a model, as I see it, is not in its mathematical representation as such, but in the assumptions that generate it. It was only 20 years later, in the second edition of my DEB book in 2000, that I was able to derive it from a short list of assumptions, like the one that the authors describe in section 6.4, but assumption 5 on the kappa-rule and 6 on mobilisation being first-order homogeneous in reserve density replaced by a partitionability assumption of reserve dynamics (see the book for its definition). It took me 10 more years, the third edition of my DEB book in 2010, to be able to replace this assumption by the weak homeostasis assumption, which also removed the need for assumption 2 on the existence of a stationary point. Since I needed the weak homeostasis assumption for several other purposes as well, such as the identification of the chemical composition of reserve and structure, I was finally satisfied with the derivation, but I fully agree with the authors that it is probably the most complex element in DEB theory. I also fully agree that their derivation from the assumptions on the kappa rule and reserve mobilisation being first order homogeneous is much simpler and also elegant.

This points to the intriguing conjecture that weak homeostasis and these two assumptions are equivalent, at least in some sense. My (more complex) derivation does not assume the kappa-rule, but I could show that kappa cannot be a function of reserve (density), but still can be a function of structure. So the 2 assumptions by the authors might be a bit stronger than weak homeostasis and weak homeostasis might follow from them. These slightly stronger assumptions probably allowed them to simplify the derivation. Lika & Kooijman [9] showed that there is a relationship between weak homeostasis and the position of reserve in metabolism, as implied by the kappa rule. This very much constrains the set of possible simple models that sport weak homeostasis. I have the feeling that, step by step, we are homing in on a fundamental understanding of metabolic organisation in an evolutionary context. For me, all this is most fascinating and what I see as a key element in the metabolism of life on earth. We could argue if their assumption 1 on reserve density is actually an assumption, or just a definition (with some basic calculus), but this is only a minor remark.

### 3. Length at birth

I also have to congratulate the authors with their expression for embryonic length as explicit function of reserve density. I only found an implicit one. If this really helps to evaluate length at birth in terms of being faster and/or more accurate is an open question since the integration constant still needs to be evaluated numerically. Future will learn.

I really enjoyed the paper by Jusup et al.

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